

Treatment-Resistant Depression in Adolescents: A Comprehensive Review

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Abstract

Treatment nonresponse in adolescent depression is a major public health problem, as untreated depression is associated with significant mortality by suicide, protracted course of illness, and recurrence into adulthood. Even with the gold-standard treatment with a Selective Serotonin Reuptake Inhibitor (SSRI) and concurrent Cognitive Behavioral Therapy (CBT), 30% to 40% will not respond to treatment, thus classified as "treatment-resistant". These depressed adolescent patients who are refractory to first-line treatments are often in such mental anguish that they are not functioning, and some have considered their only option left to end the misery is to suicide. These are the patients who are often referred to psychiatry, but the treatment options for adolescents with treatment-resistant depression are limited due to lack of research in this area. This review will consider the various treatment options that may help to alleviate the suffering of adolescents afflicted with this devastating illness, with the caveat that there are few controlled studies focused on refractory depression in adolescents.

Keywords: Depression; Treatment-resistant; Adolescent; Youth; Review

Major Depression in Youth

Major depressive disorder in youth is associated with significant mortality by suicide [1], protracted course of illness [2], high risk of recurrence [3], significant nonresponse to treatment [4,5], progression to bipolar disorder within 5 years [6-8], and high frequency of affective illness in family members [9]. Even with the gold standard treatment with an SSRI and concurrent cognitive behavioral therapy, 30% to 40% will not respond to treatment, thus classified as "treatment-resistant" [5,10,11]. A meta-analysis of published, randomized, placebocontrolled trials of SSRIs in depressed youth revealed an effect size of only 0.26 [12]. This further illustrates the poor response of SSRIs in youth depression. Treatment-resistant depression is associated with poor prognosis and high risk for suicide, indicating the need for more aggressive and clinically effective treatment than SSRIs alone can provide.

Course of Illness

The challenges of treating depressed youth throughout the course of the illness are illustrated by the following data. The mean duration of a depressive episode in youth is 32 weeks (SD=28weeks), with age of onset having an inverse relationship to time to recovery [2]. In 10% of depressed adolescents, the depressive episode lasted more than 2 years [7]. Within 5 years of the initial diagnosis, 72% of depressed youth developed recurrence [3]. The poor course of illness combined with the poor response of SSRI's in youth depression suggests that a significant number of depressed youth will not respond to first-line treatment with SSRIs.

Is Depression the Right Diagnosis?

Before considering treatment-resistant depression, the clinician should determine if major depressive disorder is the right diagnosis. Obviously, if the diagnosis of depression is incorrect, then treatments for depression will not be effective. Because several disorders can present with similar symptoms, it is important to clarify which disorder best accounts for the symptoms. The differential diagnosis for depression is extensive, and includes: bipolar depression, adjustment disorder with depressed mood, bereavement, post-traumatic stress disorder, Oppositional Defiant Disorder (ODD), Attention-Deficit Hyperactivity Disorder (ADHD), pervasive developmental disorder, and mood disorder due to a general medical condition (including substanceinduced depression). Detailed information on the clinical assessment of children and adolescents with depression can be found elsewhere [13].

Other Factors Associated with Poor Treatment Response

Other than the correct diagnosis of depression, clinicians should explore other factors which contribute to poor treatment response. Exploring other factors leading to treatment-resistant depression will also guide why a patient is not responding. Depressed adolescent patients with a history of abuse, especially physical abuse, had a poorer response to combination treatment with medication and psychotherapy [14]. These patients with a history of abuse may require specialized treatment. Adolescents with treatment-resistant depression had better treatment response if substance abuse-related impairment was low at baseline or reduced during treatment [15]. Suicidal adverse events during treatment of adolescent refractory depression were predicted by high suicidal ideations, family conflict and drug abuse at baseline. These predictors of suicidal adverse events also predict poor treatment response, and hence targeting suicidal ideations, family conflict and drug abuse can improve treatment outcomes [16]. Parent-child conflict has a bidirectional relationship with treatment outcome in adolescent treatment resistant depression [17]. Anhedonia in depressed adolescent's refractory to medication treatment predicted longer time to remission and fewer depression-free days [18]. Depression severity and subsyndromal manic symptoms predicted poor treatment response in this sample [19]. There is also suggestion that adjunctive sleep medication to SSRI treatment in this sample may be associated with poor response [20]. Interestingly, if treatment ends during school summer break,

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there was an improved treatment response [21]. Noncompliance with taking prescribed antidepressant treatment is common and associated with poor response [22]. No genetic polymorphisms were found to be associated with treatment response [23].

Options for Treatment-Resistant Depression in Youth

Current options for treatment-resistant depression in youth include optimizing the dose and duration of the current antidepressant, switching to another antidepressant within the same class, switching to another antidepressant in a different class, augmentation of the antidepressant, or combination [24]. More aggressive treatment includes Monoamine Oxidase Inhibitors (MAOI) or Electroconvulsive Therapy (ECT). Overall, minimal data exists to guide clinicians in treating refractory depression in youth.

Optimizing the Dose and Duration of the Current Antidepressant

Approximately one-third of adolescent patients with treatmentresistant depression will have achieved remission with continued treatment to 24 weeks. Those who responded by week 12 were also more likely to achieve remission [25]. In the same sample, subjects treated with citalopram and fluoxetine whose plasma concentration was equal to or greater than the geometric mean had a better treatment outcome than those whose plasma concentration was below the geometric mean. Plasma levels of paroxetine and venlafaxine was not associated with treatment outcome [26]. The data suggests optimizing the duration of antidepressant treatment, and dose optimization is suggested for paroxetine and venlafaxine. More studies are needed for optimal dosing and duration.

Switching to another Antidepressant

From data contained in a randomized controlled trial, adolescents with SSRI-resistant depression were switched to another SSRI or venlafaxine, while adding CBT, and 54.8% responded. The remission rate for a medication switch without concurrent CBT was lower at 40.5% [10]. Switching to amitryptyline or placebo in a controlled trial in a sample of adolescents with treatment resistant depression did not show any significant differences [27]. One case report provided information on MAOIs for treatment resistant depression in adolescents. Strober et al. [28] described two case reports of a 13 year old and 16 year old that was both refractory to previous antidepressant treatments, and both exhibited severe melancholic type illness characterized by psychomotor abnormalities and psychosis. The 16 year old also had an unsuccessful trial of ECT. Both patients were subsequently switched to phenelzine and titrated to a dose of 45 mg daily. Both had complete remission with phenelzinemonotherapy.

Switching to another SSRI or venlafaxine for treatment-resistant adolescent depression appears to be a viable option. MAOIs may be an option for adolescents with treatment resistant depression, but studies are lacking and the dietary restriction of an MAOI diet to avert hypertensive crisis in irreversible MAOIs may be difficult for adolescents to manage. Tricyclic antidepressants appear to not have a role in adolescent depression. More studies are needed for switching to other antidepressant classes.

Combination Strategies

No studies were found for combination strategies in treatmentresistant depression in adolescents.

Augmentation with Lithium

There are two prospective studies of lithium augmentation in adolescents with depression unresponsive to tricyclic antidepressants [29,30]. In these two studies, less than half responded to lithium augmentation, and adverse side effects were noted. Lithium did show efficacy for adolescent bipolar disorder with comorbid substance dependence, compared to placebo [31]. However, a placebo-controlled study of lithium in depressed youth at high risk for bipolarity did not show separation from placebo [32]. From these preliminary studies, lithium may have a role in treatment-resistant depression in adolescents, especially those at risk for bipolar disorder (family history of bipolar disorder, acute onset of depressive episode, and marked psychomotor retardation) [6,8].

Augmentation with Thyroid Hormone

Surprisingly, no studies are available to inform us on the utility of thyroid hormone augmentation in adolescent treatment-resistant depression.For adults with treatment resistant depression, thyroid hormone is a viable option when used to augment an antidepressant [33]. Thyroid hormone also has a better side effect profile when compared to other augmenting agents like lithium. It is worth addressing the lack of data for thyroid hormone augmentation in adolescent treatment resistant depression, even in the form of a case series or open trial.

Augmentation with Lamotrigine

A couple of case series have shown promising results for lamotrigine in treatment depression in adolescents [34,35]. In the first case series, both adolescent patients with depression refractory to antidepressants responded and remitted with the addition of lamotrigine [34]. In the second study, 6 of 12 patients with treatment resistant depression responded to lamotrigine, and one patient with depression developed benign rash with lamotrigine [35]. Although the data on lamotrigine in adolescent refractory depression are non-controlled, retrospective studies, they provide valuable information regarding safety and tolerability.

The risk of serious rash (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) associated with lamotrigine has limited its use in youth with mood disorders.Studies of lamotrigine in epilepsy indicate that the risk factors associated with serious rash and lamotrigine treatment include young age, high starting dose, rapid dose escalation, and addition of lamotrigine to valproate [36]. Starting at low doses and titrating slowly over 6 to 8 weeks may help to decrease the risk of rash.Most treatment-emergent rashes will most likely be benign and reversible.

Lamotrigine may have a role in augmenting an antidepressant for treatment resistant depression in adolescents, but randomized controlled trials are needed. Serious, life-threatening rash can be avoided by dosing low and titrating slowly over a period of several weeks. Detailed information for prescribing lamotrigine in adolescents with refractory mood disorders can be found elsewhere [37,35].

Augmentation with Antipsychotics

Two case studies provide data on augmentation with antipsychotics for adolescent treatment-resistant depression [38,39]. The first study examined 10 adolescents with major depressive disorder who did not respond to their antidepressant. When quetiapine was added to their antidepressant, 70% responded, with the most common sides effects being sedation and weight gain [38]. In the second case study, 2 adolescents with major depressive disorder were described, and both failed to respond to antidepressant treatment. The addition of quetiapine helped both patients remit, and quetiapine appeared to address the target symptoms refractory to SSRIs, which included sleep disturbance and self-harm [39]. Quetiapine may have a role as adjunctive treatment in adolescent treatment-resistant depression, being mindful of the metabolic effects of antipsychotics.

Electroconvulsive Therapy (ECT)

Some adolescents with depression fail to respond to multiple medication trials and psychotherapy, and continue to have unrelenting depressive symptoms impacting their functioning. This group of adolescents may be candidates for Electroconvulsive Therapy (ECT). Mood disorders have a response rate of 75-100% to ECT [40].

Multiple studies exist regarding ECT for adolescent treatmentresistant depression. In the only prospective study, 10 adolescents with treatment-resistant depression with psychosis were treated with ECT, with 9 responding. At 1 year follow-up, 9 were available, and 6 out of 9 were free of depressive symptoms [41].

The remaining studies are retrospective studies, most being case studies. In a case series of 6 adolescents with treatment-resistant depression, remission occurred in 5 out of 6 cases, and no cognitive impairments were noted [42]. There is also a case of successful right unilateral ultra-brief pulse electroconvulsive therapy in an adolescent with major depressive disorder with psychosis and catatonia [43]. A case report of a 13 year old female with treatment-resistant depression with psychosis responded to ECT [44]. A whole population study of ECT was conducted in adolescents, with 42 adolescents receiving ECT for major depression or psychotic depression. Mood disorders benefited most from ECT, while comorbid personality disorders predicted poor treatment outcome, and ECT only had minor adverse effects [45]. In another case series, three adolescents with major depression all responded to ECT, was well tolerated, and no relapse noted after one year follow-up [46]. Bloch et al. performed a chart review of 24 adolescent patients treated with ECT, 4 of which had depression, and 58% achieved remission [47,48] had another case series where response to ECT occurred in 5 out of 13 adolescents with major depressive disorder and 11 out of 13 adolescents with psychotic depression.In a review of all ECT studies published at the time of publication, 40 adolescents with depression had a 63% response rate [49]. ECT appears to be a viable option for treatment-resistant depression in adolescents, although controlled trials are lacking.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive Transcranial Magnetic Stimulation is emerging as a treatment option for depression in adults, and has a few studies in adolescent depression [50] conducted an open-label trial of rTMS in 9 adolescents with treatment-resistant depression, and 3 responded, and only mild side effects. From the same sample, 8 of these study participants were followed for 3 years, and found that no cognitive deterioration occurred and some subjects maintained clinical improvement after treatment [51]. Wall et al. [52] followed 7 of 8 adolescents in an open trial of rTMS for 6 months, and found rTMS to be safe and was the preferred treatment over medication for the majority of patients and their parents. In a double-blind, sham-controlled trial of rTMS in 2 adolescents with depression (one medication refractory and the other medication naïve), both subjects responded to active treatment [53]. In a case series, 2 out of 3 adolescents with treatment-resistant depression responded to ECT [54]. rTMS appears to be a promising treatment option for adolescent depression, given its relative lack of adverse effects. Although rTMS has FDA approval for adolescent treatment-resistant depression, well-designed, sham-controlled studies are needed.

Psychosocial Treatments

As mentioned earlier, adding CBT to an antidepressant led to better treatment outcomes than medicationalone [10], and combination treatment is cost effect [55]. In addition, adding CBT to an antidepressant had even better response compared to medication alone when the adolescent with depression had other comorbid disorders [56]. Also mentioned earlier was that family conflict was associated with poor treatment response, so addressing family problems is important for successful outcomes [16]. In a sample of adolescents with treatment resistant depression, those who received more than 9 sessions of adjunctive CBT were 2.5 times more likely to have treatment response than those who received 9 or fewer sessions, and those who received social skills and problem solving components were also more likely to respond [57].

For adolescent treatment resistant depression, the data suggests adding a course of CBT to antidepressant treatment, especially for those patients who have other comorbidities. In addition, the data also suggests an adequate number of CBT sessions, especially focusing on social skills and problem solving. In addition, addressing family conflict is important for having good outcomes.

Conclusion

Before considering treatments for refractory depression, the clinician needs to determine if the diagnosis of Major Depressive Disorder is correct, or if other factors are present (i.e. history of physical/sexual abuse, suicidal ideations, family conflict, substance abuse, anhedonia, depression severity, subsyndromal manic symptoms, nonadherence to treatment) that are barriers to good treatment outcomes. For treatment-resistant depression, switching to another SSRI or to venlafaxine, and adding CBT has significant data supporting this option, as many patients may respond. If this is not successful, then lithium augmentation to an antidepressant can be considered. However, if lithium is not effective or adverse effects occur, then lamotrigine can be considered, either in augmentation to an antidepressant or as monotherapy. MAOIs may also be considered, but the risk of hypertensive crisis and strict adherence to a MAOI diet may preclude its use in adolescents. ECT has a role for treatment-resistant depression, and may be the most effective option, although this is usually a last resort option, given the stigma associated with its use in young people, and uninformed government policies in some regions where the law requires multiple psychiatrists to concur on recommending ECT. Repetitive TMS is an intriguing, emerging treatment option, and given the lack of adverse effects, it is worth exploring this treatment option further. Clearly, more controlled studies are needed with regards to switching strategies, combination strategies, augmentation strategies, ECT and TMS in adolescent treatment-resistant depression.

Finally, given the complexity and multitudes of variables which may exacerbate and perpetuate a depressive episode, the clinician needs to have a broad approach and utilize various modalities to shore up the patient's inner and outer resources to help alleviate the agony and demoralization associated with unrelenting depression. Medications may not be sufficient alone to address all the external pathologies that often occur with depression. This is the value of a psychiatrist and a multidisciplinary team, utilizing a broad biopsychosocial approach [58], to deal with complex, multifactorial, treatment-resistant mental illness. Conducting a comprehensive pediatric psychophamarmacology assessment incorporating both internal and external factors can be found elsewhere [59].

Disclosure

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